



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number : **0 659 430 A1**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number : **94810733.9**

(51) Int. Cl.⁶ : **A61K 31/47**

(22) Date of filing : **19.12.94**

(30) Priority : **21.12.93 GB 9326010**

(43) Date of publication of application :
28.06.95 Bulletin 95/26

(84) Designated Contracting States :
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(71) Applicant : **SANDOZ LTD.**
Lichtstrasse 35
CH-4002 Basel (CH)
(84) **BE CH DK ES FR GB GR IE IT LI LU NL PT SE**

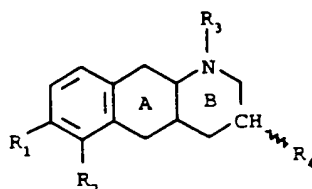
(71) Applicant : **SANDOZ-PATENT-GMBH**
Humboldtstrasse 3
D-79539 Lörrach (DE)
(84) **DE**

(71) Applicant : **SANDOZ ERFINDUNGEN**
VERWALTUNGSGESELLSCHAFT M.B.H.
Brunner Strasse 59
A-1235 Vienna (AT)
(84) **AT**

(72) Inventor : **Markstein, Rudolf**
Ernst-Reuter-Strasse 2
D-79618 Rheinfelden (DE)

(54) Use of benzo[g]quinolines in the treatment of glaucoma and for the prevention of progressive atrophy of the optic nerve.

(57) Compounds of formula I



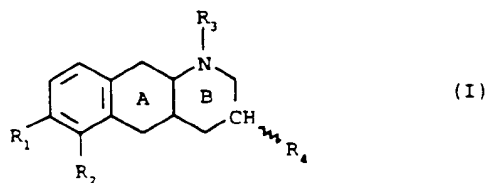
(I)

wherein A, B, R₁, R₂, R₃ and R₄ are as defined in the description, are useful for the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable.

EP 0 659 430 A1

The present invention relates to a new pharmaceutical use of 1, 2, 3, 4, 4a, 5, 10, 10a - octahydro-benzo[g]quinoline derivatives.

More particularly the present invention relates to a new pharmaceutical use for compounds of formula I



wherein

the rings A and B are trans-fused and wherein

R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-COOH$, $-CH_2OR_5$, $-CH_2CN$, $-CON(R_6)R_7$, $-CH_2SR_8$, $-NHSO_2N(R_9)R_{10}$ or $-NH-CON(R_9)R_{10}$.

R_5 is hydrogen or C_{1-3} alkyl,

R_6 is hydrogen or C_{1-3} alkyl and

R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted by halogen, methyl or methoxy or

R_6 and R_7 together are $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_2O-(CH_2)_2-$,

R_8 is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_9 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(CH_2)_4-$ or $-(CH_2)_5-$, as well as the physiologically-hydrolysable and -acceptable esters thereof.

The compounds of formula I exist in free and in salt form, e.g. as acid addition salts or, when e.g. R_4 is carboxy, as internal salts.

The compounds of formula I as well as the physiologically-hydrolysable and -acceptable esters thereof, in free or in pharmaceutically acceptable salt form, are hereinafter referred to as "the compounds".

It will be understood that the compounds include all possible individual isomers as well as racemates and other isomeric mixtures.

The compounds as well as their production process are known e.g. from U.S. Patent No. 4,565,818. This patent also discloses the use of the compounds as prolactin secretion inhibiting agents e.g. in the treatment of conditions or disorders for which reduction of prolactin secretion levels is indicated, furthermore as dopaminergic agents e.g. in the treatment of Morbus Parkinson and as dopamine receptor stimulating agents e.g. in the treatment or prophylaxis of coronary diseases.

The compounds also include the $(-)-(3\beta, 4\alpha, 10a\beta)$ -1, 2, 3, 4, 4a, 5, 10, 10a-octahydro-3-[(2-pyridylthio)methyl]-1-methyl-6-hydroxy-benzo[g]quinoline which is of formula I but is not specifically disclosed in the above mentioned U.S. patent. This compound (hereinafter referred to as compound A) in free form or acid addition salt form as well as its production process are known e.g. from U.S. Patent No. 5,262,422. This patent discloses the use of compound A in the treatment of glaucoma, Morbus Parkinson, depression and cocaine dependency.

The use of compound A in the treatment of glaucoma is based on its ability to lower intra-ocular blood pressure.

In accordance with the present invention, it has now surprisingly been found that the compounds increase the blood flow in the optic nerve.

The increase of blood flow in the optic nerve is indicated by experiments performed as described by M. Rudin and A. Sauter in Noninvasive determination of regional cerebral blood flow in rats using dynamic imaging with Gd(DTPA), Magnetic Res. in Med. 22, 32-46 (1991). In this test, rats are anesthetized with isoflurane. The femoral vein is cannulated for injection of the paramagnetic contrast agent Gd(diethylenetriaminepentaacetate). Determination of blood flow (ml/100g/min.) by NMR imaging is performed immediately before and 30 min. after s.c. drug administration. Experiments are performed double blind in groups of 7-9 animals. In a first series of experiments, the whole optic nerve is measured. In a second series, the effect on subregions of the optic nerve including the proximal part with the head of the optic nerve is determined.

In this test compound A at a dose of 0.1 mg/kg s.c. significantly improves blood flow to the proximal optic nerve by almost 30% (measured 30 min. after drug administration) whereas Timolol, the most widely used drug for the therapy of glaucoma, does not show any improvement in optic nerve perfusion at 0.5 mg/kg s.c. In the

second series of experiments, compound A markedly enhances blood perfusion in the proximal part of the optic nerve including the head and in the distal part whereas Timolol had no significant effect in both subregions of the rat optic nerve.

The compounds are therefore useful in conditions where prevention or delay of progressive atrophy of the optic nerve is desirable, for example in conditions where the visual fields are impaired and particularly in glaucoma.

It is to be noted that the compounds are useful in particular in glaucoma forms which are not characterized by an increase of the intra-ocular pressure (low tension glaucoma), in which standard glaucoma therapy including β -blockers, in particular Timolol, is useless.

It is also to be noted that the above described ability to increase the optic nerve perfusion is totally unexpected not only for the compounds which have never been suggested as antiglaucoma agents but also for compounds like compound A which exhibit intra-ocular blood pressure lowering and have therefore been suggested for the treatment of glaucoma.

Drugs which like compound A and unlike Timolol improve both elevated intra-ocular pressure and impaired blood flow in the optic nerve are expected to possess disease-modifying properties, which is of particular interest.

For the above-mentioned indications the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.01 to about 1 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.25 to about 10 mg of a compound according to the invention conveniently administered, for example, in divided doses up to four times a day.

The compounds may be administered in any usual manner, e.g. orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injection solutions or suspensions.

For the treatment of glaucoma, the compounds are preferably applied topically to the eye in ca. 0.002 to ca. 0.02 % ophthalmological solutions. The ophthalmic vehicle is such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye. The pharmaceutically acceptable ophthalmic vehicle may be e.g. an ointment, vegetable oil, or an encapsulating material. Compound A is suitably administered in form of its hydrochloride.

The present invention also provides pharmaceutical compositions comprising the compounds in association with at least one pharmaceutical carrier or diluent for use in the treatment of glaucoma. Such compositions may be manufactured in conventional manner. Unit dosage forms may contain for example from about 0.05 mg to about 5 mg of the compound.

The invention further provides the use of a compound according to the invention for the manufacture of a pharmaceutical composition for the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable, in particular glaucoma.

The invention furthermore provides a method for the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable, in particular glaucoma, in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound according to the invention.

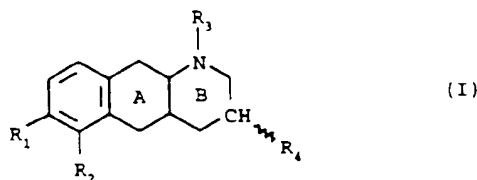
Example: Eye drops

An injection solution containing the ingredients indicated below is prepared by conventional techniques and is useful in the treatment of glaucoma:

Composition	mg/ml
Compound A in hydrochloride form	1.107
Glycerol	25.0
Benzalkonium chloride	0.105
Hydroxypropylmethylcellulose	1.0
Water for injection to	1.0 ml

Claims

1. The use of a compound of formula I



wherein

the rings A and B are trans-fused and wherein

R_1 and R_2 are each independently hydrogen, hydroxy or methoxy, with the proviso that R_1 and R_2 may not both be hydrogen;

R_3 is hydrogen or C_{1-4} alkyl;

R_4 is $-COOH$, $-CH_2OR_5$, $-CH_2CN$, $-CON(R_6)R_7$, $-CH_2SR_6$, $-NHSO_2N(R_9)R_{10}$ or $-NH-CON(R_9)R_{10}$,

R_5 is hydrogen or C_{1-3} alkyl,

R_6 is hydrogen or C_{1-3} alkyl and

R_7 is hydrogen, C_{1-3} alkyl, phenyl or pyridyl, said phenyl or pyridyl being optionally substituted by halogen, methyl or methoxy or

R_6 and R_7 together are $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_2-O-(CH_2)_2-$,

R_8 is C_{1-4} alkyl or pyridyl, said pyridyl being optionally substituted by halogen, methyl or methoxy, and

R_9 and R_{10} are each independently hydrogen or C_{1-3} alkyl or together are $-(CH_2)_4-$ or $-(CH_2)_5-$, as well as of the physiologically-hydrolysable and -acceptable esters thereof, in free or in pharmaceutically acceptable salt form,

for the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable.

2. The use according to claim 1, for the treatment of glaucoma.
3. The use according to claim 1, wherein the compound of formula I is the $(-)-(3\beta, 4\alpha, 10a\beta)$ -1,2,3,4,4a,5,10,10a-octahydro-3-[(2-pyridylthio)methyl]-1-methyl-6-hydroxy-benzo[g]quinoline in free form or acid addition salt form.
4. A method for the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable, in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound according to claim 1.
5. A method according to claim 4, for the treatment of glaucoma.
6. A method according to claim 4, for the treatment of low tension glaucoma.
7. The use of a compound according to claim 1, for the manufacture of a pharmaceutical composition for the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable.
8. The use according to claim 7 for the manufacture of a pharmaceutical composition for the treatment of glaucoma.
9. A pharmaceutical composition which incorporates as active agent a compound according to claim 1, for use in the treatment of conditions where prevention or delay of progressive atrophy of the optic nerve is desirable.
10. A pharmaceutical composition according to claim 9, for use in the treatment of glaucoma.



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 94 81 0733
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	DE-A-41 14 325 (SANDOZ-PATENT-GMBH) 5 November 1992 * the whole document *	1-10	A61K31/47
D	& US-A-5 262 422 ---		
D,X	US-A-4 565 818 (R. NORDMANN ET AL.) 21 January 1986 * the whole document *	9,10	
A	---	1-8	
A	BR. J. OPHTHALMOL., vol.77, no.12, December 1993 pages 785 - 788 M. GROCHOWICKI 'Ophthalmic results in patients with macroprolactinomas treated with a new prolactin inhibitor CV 205-502' * the whole document *	1-10	
A	US-A-4 405 626 (M.R. JOHNSON) 20 September 1983 * abstract *	1-10	
A	EP-A-0 257 887 (HOUSTON BIOTECHNOLOGY INCORPORATED) 2 March 1988 * the whole document *	1-8	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely:</p> <p>Claims searched incompletely:</p> <p>Claims not searched:</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		22 March 1995	Stierman, B
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p>		<p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>A : member of the same patent family, corresponding document</p>	

EP FORM 1503 (12.92) (P06C01)



EP 94 81 0733

- C -

Remark : Although claims 4-6 are directed to a method of treatment of the human/animal body (Art. 52(4) EPC) the search has been carried out and based on the alleged effects of the compound/composition.